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Characteristics, comorbidities, and correlates of atypical depression: Evidence from the UK Biobank Mental Health Survey

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Abstract:	Background: Depression is a heterogeneous disorder with multiple aetiological pathways and multiple therapeutic targets. This study aims to determine whether atypical depression (AD) characterized by reversed neurovegetative symptoms is associated with a more pernicious course and a different sociodemographic, lifestyle, and comorbidity profile than nonatypical depression (nonAD). Methods: Among 157,366 adults who completed the UK Biobank Mental Health Questionnaire (MHQ), N=37,434 (24%) met the DSM-5 criteria for probable lifetime major depressive disorder (MDD) based on the Composite International Diagnostic Interview Short Form. Participants reporting both hypersomnia and weight gain were classified as AD cases (N=2,305), and the others as nonAD cases (N=35,129). Logistic regression analyses were conducted to examine differences between AD and nonAD in depression features, sociodemographic and lifestyle factors, lifetime adversities, psychiatric and physical comorbidities. Results: Persons with AD experienced an earlier age of depression onset, longer, more severe and recurrent episodes, and higher help-seeking rates than nonAD persons. AD was associated with female gender, unhealthy behaviours (smoking, social isolation, low physical activity), more lifetime deprivation and adversity, higher rates of comorbid psychiatric disorders, obesity, cardiovascular disease (CVD), and metabolic syndrome. Sensitivity analyses comparing AD persons with those having typical neurovegetative symptoms (hyposomnia and weight loss) revealed similar results. Conclusions: These findings highlight the clinical and public health significance of AD as a chronic form of depression, associated with high comorbidity and lifetime adversity. Our findings have implications for predicting depression course and comorbidities, guiding research on aetiological mechanisms, planning service use and informing therapeutic approaches.

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Abstract

Background: Depression is a heterogeneous disorder with multiple aetiological pathways and multiple therapeutic targets. This study aims to determine whether atypical depression (AD) characterized by reversed neurovegetative symptoms is associated with a more pernicious course and a different sociodemographic, lifestyle, and comorbidity profile than nonatypical depression (nonAD).

Methods: Among 157,366 adults who completed the UK Biobank Mental Health Questionnaire (MHQ), N=37,434 (24%) met the DSM-5 criteria for probable lifetime major depressive disorder (MDD) based on the Composite International Diagnostic Interview Short Form. Participants reporting both hypersomnia and weight gain were classified as AD cases (N=2,305), and the others as nonAD cases (N=35,129). Logistic regression analyses were conducted to examine differences between AD and nonAD in depression features, sociodemographic and lifestyle factors, lifetime adversities, psychiatric and physical comorbidities.

Results: Persons with AD experienced an earlier age of depression onset, longer, more severe and recurrent episodes, and higher help-seeking rates than nonAD persons. AD was associated with female gender, unhealthy behaviours (smoking, social isolation, low physical activity), more lifetime deprivation and adversity, higher rates of comorbid psychiatric disorders, obesity, cardiovascular disease (CVD), and metabolic syndrome. Sensitivity analyses comparing AD persons with those having typical neurovegetative symptoms (hyposomnia and weight loss) revealed similar results.

Conclusions: These findings highlight the clinical and public health significance of AD as a chronic form of depression, associated with high comorbidity and lifetime adversity. Our findings have implications for predicting depression course and comorbidities, guiding research on aetiological mechanisms, planning service use and informing therapeutic approaches.

Introduction

Major depressive disorder (MDD) is a highly prevalent, burdensome, and heterogeneous mental health disorder. This heterogeneity presumably represents multiple causal pathways and consequently multiple therapeutic targets. The development of novel therapeutic agents would benefit from the identification of more homogeneous depression subtypes, which could be derived based on a triangulation of clinical phenotypes, risk factors and biology (Harald and Gordon, 2012). One such subtype is depression with atypical features.

Atypical depression (AD) is an intriguing clinical phenomenon that has been recognised since the late 1950s and has evolved as a syndrome of varying definitions (Davidson and Thase, 2007, Lojko and Rybakowski, 2017). The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for AD requires mood reactivity and at least two of the following symptoms: increased appetite or weight gain, hypersomnia, leaden paralysis and interpersonal rejection sensitivity (American Psychiatric Association, 2013). Whereas most clinical studies adopt the DSM criteria for AD, community studies tend to classify AD based purely on reversed neurovegetative symptoms (i.e., hypersomnia and increased appetite/weight gain) (Lee *et al.*, 2009, Levitan *et al.*, 1997, Matza *et al.*, 2003), for a number of reasons. First, reversed neurovegetative symptoms are easier to operationalise in epidemiological studies than other DSM criteria for atypicality. Second, several studies have questioned the evidential support for the role of mood reactivity and interpersonal rejection sensitivity in the diagnosis of atypical depression (Benazzi, 2002b, Parker and Thase, 2007). Third, reversed neurovegetative symptoms were found to be highly specific (90.5%), and have good positive predictive value (86.1%) for DSM-defined AD (Benazzi, 2002a). Fourth, research comparing AD based on reversed neurovegetative symptoms with AD based on the full DSM criteria found similar associations with a range of sociodemographic characteristics and comorbidities (Benazzi, 2002a). Lastly, AD based on reversed neurovegetative symptoms

may be more strongly associated with external validating characteristics of AD (e.g., gender, bipolar disorder, family history of mania) than other atypical symptoms of depression (Angst *et al.*, 2006).

There is growing interest in understanding the epidemiological, neurobiological, and genetic underpinnings of AD (Lojko and Rybakowski, 2017). Evidence from clinical and community-based studies suggest differences between AD and nonAD in sociodemographic factors, depression features, comorbidities, biomarkers, polygenic risk, and treatment response. Atypical depression is more strongly associated with female gender (Angst *et al.*, 2007, Lee *et al.*, 2009, Matza *et al.*, 2003), younger age of depression onset, greater symptom severity, more depression episodes, greater functional impairment (Agosti and Stewart, 2001, Blanco *et al.*, 2012, Nierenberg *et al.*, 1998, Stewart *et al.*, 1993), and more adverse life events (Matza *et al.*, 2003, Withers *et al.*, 2013). AD is also associated with higher rates of psychiatric comorbidity such as bipolar, anxiety, addictions, binge eating and psychotic disorders (Agosti and Stewart, 2001, Angst *et al.*, 2002, Blanco *et al.*, 2012, Lee *et al.*, 2009, McGinn *et al.*, 2005), higher Body Mass Index (BMI) (Lasserre *et al.*, 2014) as well as polygenic risk scores for BMI and triglycerides (Milaneschi *et al.*, 2016), higher rates of metabolic syndrome, inflammation, and leptin dysregulation (Lamers *et al.*, 2016a, Lamers *et al.*, 2013, Milaneschi *et al.*, 2017a), and greater heritability than nonAD (Lamers *et al.*, 2016b). Existing evidence is limited by the use of different comparison groups across studies: non-atypical depression (i.e., depression without reversed neurovegetative symptoms) (e.g., Agosti and Stewart, 2001, Lee *et al.*, 2009, Matza *et al.*, 2003), typical depression with both neurovegetative symptoms (i.e., hyposomnia and reduced appetite and/or weight loss) (e.g., Blanco *et al.*, 2012, Levitan *et al.*, 1997) or just one neurovegetative symptom (i.e., appetite loss/weight loss) (e.g., Milaneschi *et al.*, 2016), or melancholic depression (e.g., Angst *et al.*, 2007, Lamers *et al.*, 2016a).

An important proportion of persons who experience common mental health disorders such as depression do not receive clinical assessment or treatment. Conclusions from clinical studies on depression subtypes suffer from poor external validity and are not powered enough to consider multiple outcomes. Community-based psychiatric epidemiology studies are needed to help characterize depression phenotypes based on lifetime self-reported symptoms. Existing evidence from studies that examined atypical depression with reversed neurovegetative is limited by small sample size (Benazzi, 2002a, Levitan *et al.*, 1997, Matza *et al.*, 2003), a focus on current or recent rather than lifetime depression episodes (Lee *et al.*, 2009), the use of different comparison groups, and data availability on a relatively limited number of comorbidities and correlates of atypical depression.

The UK Biobank MHQ is one of the largest mental health surveys ever conducted among middle-aged and older adults (Davis *et al.*, 2018). Given the diversity of mental health measures and linkages to UKB baseline assessments, this study offers the opportunity to replicate and extend evidence on the sociodemographic, clinical, lifestyle, and comorbidity profile of persons with lifetime AD characterized by reversed neurovegetative symptoms compared to those with nonAD, or those with typical neurovegetative symptoms. This foundational work could form the basis for exploring biomarker and genetic correlates of atypical depression in the UK Biobank, and could further guide intervention approaches.

Method

Subjects

The UK Biobank is a well-characterized cohort of over half a million participants aged 40 to 69 at baseline (2007-2010), providing the potential for a detailed examination of the interplay between genetic, biological, lifestyle, and environmental factors and the risk of physical and mental health disorders, which is further enhanced by planned follow-up assessments and linkages to routine healthcare records. A comprehensive description of the UK

Biobank cohort, study design, and assessments has been published elsewhere (Sudlow *et al.*, 2015). An online Mental Health Questionnaire (MHQ) was developed and implemented into the UK Biobank web questionnaire platform with the aim to identify mental health disorders either based on self-reported symptoms matching psychiatric diagnostic criteria or based on other self-reported psychiatric diagnosis (Davis *et al.*, 2018). Participants who volunteered to take part in the study had higher socioeconomic status, healthier lifestyle and fewer health conditions than the general population (Davis *et al.*, 2018, Fry *et al.*, 2017). Out of 503,328 participants who completed the baseline UK Biobank assessments, 339,092 (67.4%) participants received an email invitation to complete the MHQ, with 157,366 of those emailed (46.4%) responding by August 2017. Approximately 37,434 (23.8%) of those who completed the MHQ met the criteria for a lifetime diagnosis of MDD and were included in the current study.

Measures

Data were accessed through standard UKB procedures (access number 34553, Matthew Hotopf and collaborators) in July 2018. Case and control criteria for psychiatric disorders are presented in Supplementary Table 7 (Davis *et al.*, 2018). All other variables were assessed using specific sets of questions and possible answers as detailed in Supplementary Table 6. All information on lifetime mental health symptoms, psychiatric diagnoses, and adverse life events (i.e., childhood, adulthood and catastrophic trauma) was collected during the MHQ assessments conducted in 2016-2017. Data on sociodemographic characteristics (i.e., age, gender, education, income, house ownership), lifestyle factors (i.e., smoking, physical activity, loneliness, social isolation), and physical comorbidities (i.e., longstanding illness, CVD, BMI, metabolic syndrome) were collected during the baseline UK Biobank assessments between 2006 and 2010.

Lifetime MDD was assessed using the Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler and Ustun, 2004) and it required at least one core symptom of depression (i.e., persistent sadness or loss of interest) and at least four additional symptoms (i.e., tired or low energy, weight change, sleep change, trouble concentrating, feeling worthless, thinking about death), for a period of at least two weeks, representing a change from usual and associated with some or a lot of impairment. The CIDI-SF has been designed and shown to have good comparability with the full WHO Composite International Diagnostic Interview, although it shares with many screening tools a lack of specificity in community samples. Previous studies suggest that CIDI-SF has good sensitivity (89.6%) and specificity (93.9%), with 93.2% of respondents being classified as probable MDD cases on both the CIDI-SF and the full CIDI interview when these instruments were administered as part of the same survey (Kessler and Ustun, 2004). However, independent validation studies reported that CIDI-SF is highly sensitive but not very specific (i.e., identifies a high number of false positives), and recommended that CIDI-SF would be a useful general screening measure for depression, but not a highly accurate tool for prevalence estimates (Patten, 1997, Sunderland *et al.*, 2011). Online CIDI-SF screening for recurrent MDD had a 81.8% validation rate by the SCID interview, whereas the validation rate for single episode MDD was 87.6% (Levinson *et al.*, 2017). The lifetime version of the CIDI-SF asked about symptoms experienced during the worst ever depression episode. Consistent with previous studies (Benazzi, 2002a, Blanco *et al.*, 2012, Lee *et al.*, 2009), the presence of reversed neurovegetative symptoms was used to differentiate between AD and nonAD. Participants reporting both hypersomnia and weight gain were classified as AD cases (N=2,305), and the others classified as nonAD cases (N=35,129).

Diagnostic criteria based on self-report questionnaires were also evaluated for generalised anxiety disorder, post-traumatic stress disorder (PTSD), and bipolar affective disorder (i.e., wider bipolar disorder, bipolar I disorder, and bipolar II disorder), as defined in

Supplementary Table 7. Of note, there is limited agreement about the definition of bipolar II disorder in MHQ. Whereas the DSM-IV criteria require symptoms present for minimum four days, the MHQ criteria require symptoms present for at least 1 week, so it could be predicted to miss some cases. Also, given that bipolar II disorder does not require disruption from symptoms, self-reported symptoms may reflect normal emotional experiences, resulting in an increased number of false positives (Davis *et al.*, 2018). Other psychiatric comorbidities were defined by asking participants if they have ever been diagnosed with a psychiatric disorder by a mental health professional, including psychotic disorders (i.e., schizophrenia, other psychosis), anxiety disorders (i.e., panic attacks, agoraphobia, social phobia), obsessive compulsive disorder (OCD), eating disorders (i.e., anorexia nervosa, bulimia nervosa, binge-eating disorder), attention deficit hyperactivity disorder, autism spectrum disorder and personality disorders. Participants also self-reported any lifetime addiction (including substances and behaviours), substance dependence (including medication and illicit or recreational drugs), and alcohol dependence. They also reported a history of self-harm, with or without suicide intent (see Supplementary Table 6).

Participants were classified as having metabolic syndrome if they had a waist circumference ≥ 102 cm or above for males and ≥ 88 cm for females, and a combination of any two of the following: 1) *hypertension* defined as a) average systolic blood pressure ≥ 140 over three assessment occasions and/or b) average diastolic blood pressure ≥ 90 over three assessment occasions, and/or c) hypertension medication prescription, and/or d) a clinical diagnosis of hypertension according to participant self-report; 2) *diabetes* defined as a) diabetes medication prescription; b) a clinical diagnosis of diabetes according to participant self-report; and 3) *hypercholesterolemia* defined as a) statins medication prescription; b) a clinical diagnosis of hypercholesterolemia according to participant self-report.

Statistical Analysis

Univariate logistic regression models were conducted to examine differences between persons with AD (i.e., meeting the criteria for MDD + hypersomnia and weight gain) and persons with nonAD (i.e., meeting the criteria for MDD without hypersomnia and weight gain) in sociodemographic factors (i.e., age, gender, education, income, house ownership). Multivariable logistic regression models were used to examine differences between nonAD and AD in lifestyle factors, lifetime adversities, depression features, and comorbidities, controlling for age and gender, and then also for socioeconomic factors. Sensitivity analyses were conducted to compare persons with AD (as defined above) and those with typical vegetative symptoms (i.e., meeting the criteria for MDD + reporting weight loss, and either waking up too early or trouble falling asleep).

Results

Tetrachoric correlations between CIDI-SF depressive symptoms among persons with lifetime probable MDD are presented in Supplementary Table 5.

Prevalence of depression subtypes and associations with sociodemographic factors

The AD group (N=2,305) had a mean age of 59.8 years old and 75% were female, whereas the nonAD group (N=35,129) had a mean age of 62.4 years old and 68% were female. Persons with AD had lower income, and they were less likely to own a mortgage or the outright for their home than persons with nonAD (see Table 1).

Depression course

The mean age of depression onset was 31.9 in the AD group and 35.5 in the nonAD group. Compared to persons with nonAD those with AD experienced more severe, recurrent, and lengthy depression episodes. For instance, 24% of persons with AD experienced a depression episode lasting over 2 years compared to 13% of persons with nonAD; 39% of persons with AD experienced a severe depression episode compared to 14% of persons with

nonAD (i.e., depression was considered severe when all eight CIDI-SF symptoms were endorsed). Persons with AD were more likely to seek professional help for depression (see Table 2).

Lifestyle factors and lifetime adversities

Persons with atypical depression were more likely to be smokers, they reported higher rates of social isolation and loneliness, and lower rates of moderate physical activity. Moreover, they were more likely to experience a variety of adverse events over their life course, including emotional, physical and sexual abuse during childhood and adulthood, financial difficulties and catastrophic trauma (see Table 3).

Psychiatric comorbidities

Persons with AD were more likely to experience a probable lifetime psychiatric disorder of GAD, bipolar I and wider bipolar disorder (but not bipolar II), and they were more likely to meet the criteria for PTSD. Also, persons with AD were more likely to self-report a lifetime psychiatric diagnosis, including schizophrenia, agoraphobia, social phobia, panic attacks, OCD, autism spectrum disorders, ADHD, substance and alcohol dependence, personality disorders, and self-harm. The odds of binge eating disorder were 4.6 higher among persons with AD compared to those with nonAD. Persons with AD had lower rates of anorexia and similar rates of bulimia as those with nonAD (see Table 4).

Physical comorbidities

Persons with AD had higher odds of long-standing illness, CVD, and metabolic syndrome; they scored higher on each of the components of the metabolic syndrome: diabetes (OR = 2.32, 95% CI [1.94-2.78], hypertension (OR = 1.65, 95% CI [1.49-1.82] and hypercholesterolemia (OR = 1.49, 95% CI [1.30-1.71]. BMI scores were significantly higher among persons with AD (Mean = 30.7, SD = 5.9) compared to those with nonAD (Mean =

27.0, SD = 4.9), with a greater proportion of overweight and obese persons in the AD group (see Table 4).

Sensitivity analyses

All differences between AD and nonAD in depression features, sociodemographic and lifestyle factors, lifetime adversities, psychiatric and physical comorbidities remained statistically significant after accounting for socioeconomic status (i.e., income, house ownership, education), except for personality disorders and smoking status.

The requirement of participants in the AD group to have two specific symptoms (hypersomnia and weight gain) may have resulted in the selection of a more severe sample, since severity in this definition is defined by number of symptoms. Therefore, we conducted a set of sensitivity analyses that compared persons with AD (i.e., hypersomnia and weight gain) with those meeting the criteria for depression with typical neurovegetative symptoms (i.e., weight loss and hyposomnia: waking too early or trouble falling asleep), thereby requiring two specific symptoms in both samples. Among depressed persons with typical neurovegetative symptoms 24% had severe depression, versus 39% of AD persons. These sensitivity analyses revealed a similar pattern of findings (in terms of direction, magnitude, and statistical significance of the effect) as the main analyses using nonAD as the comparison group, except for gender differences and personality disorder differences which were no longer statistically significant (see Supplementary Tables 1-4).

Discussion

This study ascertains AD based on reversed neurovegetative symptoms as a valid entity in a large community-based sample, and it informs on differences between AD and nonAD in terms of sociodemographic, lifestyle, and clinical characteristics, lifetime psychiatric and

physical comorbidities. These findings highlight the clinical and public health significance of the AD classifier.

The previously reported prevalence of AD based on reversed neurovegetative symptoms was in the range of 11-16% (Horwath *et al.*, 1992, Levitan *et al.*, 1997). In our study about 6.5% (N=2305) of persons with MDD met the criteria for AD. Given that the UK Biobank sample is not representative for the general population (i.e., healthy volunteer effect) these results should not be interpreted as estimates of AD prevalence in the wider community, but rather as proportions within the sample. Building on prior evidence, our findings suggest that persons with AD have a younger age of depression onset (Blanco *et al.*, 2012, Koyuncu *et al.*, 2015, Matza *et al.*, 2003, Novick *et al.*, 2005, Thase, 2007), longer (Angst *et al.*, 2002, Posternak and Zimmerman, 2002), more severe (Blanco *et al.*, 2012, Novick *et al.*, 2005), and recurrent episodes (Blanco *et al.*, 2012, Koyuncu *et al.*, 2015), and higher help seeking rates (Angst *et al.*, 2006, Lee *et al.*, 2009, Matza *et al.*, 2003) compared to persons with nonAD.

Consistent with previous evidence, we found that depression with atypical features was associated with female gender (Agosti and Stewart, 2001, Benazzi, 2002a, Blanco *et al.*, 2012, Lee *et al.*, 2009) and with unhealthier behaviours, such as reduced physical activity (Glaus *et al.*, 2013), social isolation (Agosti and Stewart, 2001), and smoking. Previously, Koyuncu *et al.* (2015) found higher rates of social anxiety and avoidance among individual with AD features. These findings are not surprising given that hypersensitivity to criticism or rejection is a characteristic feature of AD which can lead individuals to avoid interpersonal activity and social situations. Consistent with prior reports (Blanco *et al.*, 2012), we found that persons with AD were more likely to experience socio-economic disadvantage than persons with nonAD. Previously, childhood trauma, in the form of physical or sexual abuse, was associated with the reversed neurovegetative symptoms of AD (Matza *et al.*, 2003). Our findings add to the existing literature by showing that AD is associated with a range of emotional, physical, sexual, financial and catastrophic adversities across the lifespan.

The diversity of mental health assessments in the MHQ offered the opportunity to examine associations between AD and a wide range of lifetime psychiatric comorbidities. Our findings on psychiatric comorbidities are consistent with a large community-based study on lifetime atypical depression conducted in the United States (Blanco *et al.*, 2012). We found that persons with AD had higher rates of bipolar I and wider bipolar disorder than those with nonAD, but differences in bipolar II disorder were only marginally significant. An association between AD and bipolar I but not bipolar II was previously reported by Blanco *et al.* (2012), but most existing evidence supports a strong association between AD and bipolar II disorder (Agosti and Stewart, 2001, Akiskal and Benazzi, 2005, Angst *et al.*, 2002, Benazzi, 2002a, Lee *et al.*, 2009). The failure to replicate this finding in our study may be due to the arguable definition of bipolar II disorder in the MHQ (Davis *et al.*, 2018) (see Supplementary Table 7). Our findings are consistent with prior evidence suggesting higher rates of anxiety disorders (i.e., generalised anxiety, panic attacks, social phobia, agoraphobia) (Angst *et al.*, 2002, Blanco *et al.*, 2012, Horwath *et al.*, 1992, Koyuncu *et al.*, 2015, Matza *et al.*, 2003, Novick *et al.*, 2005, Sullivan *et al.*, 1998), OCD (Perugi *et al.*, 1998), psychotic disorders (Blanco *et al.*, 2012), binge eating (Angst *et al.*, 2006, Angst *et al.*, 2002), substance and alcohol dependence (Blanco *et al.*, 2012), and personality disorders (McGinn *et al.*, 2005) among persons with AD. Additionally, we found that persons with AD had higher rates of ADHD, autism, and self-harm, but they were not more likely than persons with nonAD to self-harm with suicide intent. A study conducted in Hong Kong reported a trend for higher rates of suicidal ideation and suicidal attempt in AD (Lee *et al.*, 2009).

The association between MDD and obesity is supported by widespread evidence, including findings from a recent UK Biobank study (Ul-Haq *et al.*, 2014). Emerging evidence suggests higher rates of obesity and metabolic syndrome among persons meeting the full DSM-IV criteria for atypical depression (Lasserre *et al.*, 2014) and among those meeting only the hyperphagia and weight gain criteria (Lamers *et al.*, 2013). Recent evidence also suggests a

genetic overlap between obesity and an AD subtype characterized by increased appetite and weight gain (Milaneschi *et al.*, 2017b). We found that among persons with AD characterized by reversed neurovegetative symptoms 49% were obese (BMI ≥ 30) and 36% were overweight (BMI ≥ 25), whereas among nonAD persons 22% were obese and 39% were overweight. Biological theories propose that leptin dysregulation and inflammation underlie the association between obesity and atypical depression, whereas psychological theories suggest that the interpersonal rejection sensitivity that is characteristic to AD is accompanied by emotional dysregulation mechanisms and self-consolatory behaviours such as comfort eating (for a review see Lojko and Rybakowski, 2017). With regard to the association between atypical depression and CVD, prior evidence is mixed, with some findings suggesting a higher CVD incidence among AD persons with reversed neurovegetative symptoms (Case *et al.*, 2018), whereas other reports support and association between atypical depression and cardiovascular risk factors but not CVD diagnosis (Niranjan *et al.*, 2012). Our findings confirm higher rates of CVD among AD persons. It should be noted that information on physical comorbidities was collected during the UK Biobank baseline assessments conducted approximately seven years before the MHQ. The relation between depression and comorbidities such as obesity, metabolic syndrome and CVD is likely multifaceted and bidirectional. Given that our study focused on lifetime depression it was not possible to determine whether physical disorders occurred before or after the atypical depression episode, hence not allowing inferences about the direction of the effect.

Finally, it is worth noting that the same pattern of results emerged when comparing persons with AD (hypersomnia and weight gain) with those reporting the opposite/typical neurovegetative symptoms (hyposomnia and weight loss), suggesting that the observed findings are not simply attributable to the selection of more severe depression cases in the AD group.

Strengths and limitations

The current study based on the UK Biobank MHQ dataset provided a unique opportunity to identify differences between typical and atypical depression in illness course, sociodemographic and lifestyle factors, adverse life events and comorbidities in a large community sample of middle aged and older adults. However, there are also a number of limitations. First, the UK Biobank is not representative for the overall population as there is a degree of 'healthy volunteer' selection bias, with higher participation rates among females, older, better educated, less deprived, and healthier participants than the general population (Fry *et al.*, 2017). Furthermore, participants who completed the MHQ have higher educational and occupational attainment, and lower rates of longstanding illness, disability and smoking than the overall UK Biobank cohort and the general population (Davis *et al.*, 2018). It has been previously shown that non-response to MHQ is weakly related to depression status, with 20.3% of the MHQ respondents versus 23.6% of the MHQ non-respondents reporting feeling depressed during the last two weeks preceding the baseline UKB assessment (conducted approximately 7 years before the MHQ), and 5.2% of the MHQ respondents versus 7.1% of the MHQ non-respondents reporting a lifetime medical diagnosis of depression during the baseline UK Biobank assessments (Davis *et al.*, 2018). It was not possible to compare non-response rates between the AD and the nonAD group because baseline UK Biobank assessments did not include questions allowing a characterization of depression subtypes. It is possible that the healthy volunteer selection bias in the UK Biobank MHQ may have resulted in an underestimation of the prevalence of AD in our sample, given the higher depression severity among AD patients and the fact that severely depressed persons were less likely to complete the MHQ. Second, due to the cross-sectional nature of this study, our findings do not allow to determine whether life events and comorbidities occurred before, during or after the typical versus atypical depression episode. Moreover, it was not possible to determine whether

participants experienced lifetime fluctuations between typical and atypical depression episodes as suggested by previous reports (Angst *et al.*, 2007, Levitan *et al.*, 1997). Third, psychiatric conditions were assessed using self-reported symptoms and self-reported diagnosis, so they represent probable, rather than definitive, clinical diagnoses (Davis *et al.*, 2018). CIDI-SF does not contain questions assessing appetite changes, but only weight changes. We had no specific cut-off points to quantify the weight gain or the number of hours of sleep per night during the worst depression episode. Therefore, we cannot exclude the possibility that self-reported symptoms may be subject to recall bias or may be affected by other medical conditions. Finally, our assessments did not capture other atypical symptoms such as leaden paralysis, interpersonal rejection sensitivity or mood reactivity. Nevertheless, our findings based on a definition of atypical depression characterized by reversed neurovegetative symptoms are remarkably consistent with prior evidence from both clinical and community-based studies.

Conclusions and implications

The symptom heterogeneity of depression, in conjunction with etiological and methodological heterogeneity, hinders progress in the diagnosis, prognosis and treatment of depression. A better characterization of the AD subtype in terms of symptom profile, clinical course, neurobiology and comorbidities could inform personalized medicine approaches (Korte *et al.*, 2015). Our findings suggest that criteria such as early age of onset, chronicity, and recurrence should be considered as part of the clinical picture of AD. The pernicious course of AD and the high psychiatric comorbidity profile have important implications for health care utilization and costs. In clinical practice, focusing on the identification of atypical features could inform prognosis, and treatment planning. Future research should determine to what extent the early identification and treatment of atypical depression symptoms may prevent or delay the onset of physical comorbidities. Forthcoming availability of biomarker data in the UK Biobank will provide the opportunity to further examine metabolic and inflammatory

biomarkers in atypical depression. The high rate of obesity and metabolic syndrome among atypically depressed persons could have implications for treatment selection (i.e., antidepressant treatment that does not influence weight gain). Patients with different/opposite depression symptoms likely have different neurobiological disturbances and could benefit from better tailored therapeutic approaches. Although findings on differential treatment response are largely controversial (Harald and Gordon, 2012), recent evidence suggests larger treatment response to exercise in AD compared to nonAD (Rethorst *et al.*, 2016), a superior effect of cognitive therapy compared to paroxetine treatment in reducing atypical-vegetative symptoms (Fournier *et al.*, 2013), and the potential of pharmacotherapy and cognitive therapy continuation to reduce relapse rates among persons with AD (Jarrett *et al.*, 2000). Clinical trials should further determine the effectiveness of lifestyle interventions and therapeutic agents targeting metabolic and inflammatory pathways in AD. This knowledge could inform treatment guidelines and facilitate a better management of persons with atypical symptoms of depression.

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Table 1. Sociodemographic differences between persons with atypical depression and those with non-atypical depression

		Atypical Depression N=2,305		Non-Atypical Depression N=35,129			
		n	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Age	45to54	625	27.1	6,520	18.6	Ref	P < 0.001
	55to64	1,051	45.6	13,758	39.2	0.79(0.72-0.88)	P < 0.001
	65to74	585	25.4	13,154	37.4	0.46(0.41-0.52)	P < 0.001
	75Plus	44	1.9	1,697	4.8	0.27(0.20-0.37)	P < 0.001
Gender	Female	1,732	75.1	24,083	68.6	Ref	
	Male	573	24.9	11,046	31.4	0.95(0.94-0.96)	P < 0.001
Education	None	113	4.9	2,040	5.9	Ref	
	Other (vocational)	89	3.9	1,788	5.1	0.90(0.68-1.19)	P = 0.46
	Secondary school	705	31.0	10,006	28.8	1.27(1.04-1.56)	P < 0.05
	A level	397	17.4	4,982	14.3	1.44(1.16-1.78)	P < 0.01
	Degree	974	42.8	15,965	45.9	1.10(0.90-1.35)	P = 0.34
Income	<£18,000	442	21.0	5,311	16.6	Ref	
	£18,000-30,000	511	24.3	7,642	23.9	0.80(0.70-0.92)	P < 0.01
	£30,000-52,000	597	28.4	9,158	28.7	0.78(0.69-0.89)	P < 0.001
	£52,000-100,000	457	21.8	7,823	24.5	0.70(0.61-0.80)	P < 0.001
	>£100,000	94	4.5	2,013	6.3	0.56(0.45-0.71)	P < 0.001
House ownership	Rent social	197	8.8	1,464	4.2	Ref	
	Rent private	120	5.4	1,124	3.3	0.79(0.62-1.01)	P = 0.06
	Own mortgage	1,078	48.2	15,230	44.3	0.53(0.45-0.62)	P < 0.001
	Own outright	839	37.6	16,562	48.2	0.38(0.32-0.44)	P < 0.001

Table 2. Differences in depression age of onset, severity, recurrence, episode duration, and help seeking between persons with atypical depression and those with non-atypical depression

	Atypical Depression N=2,305		Non-Atypical Depression N=35,129			
	n	**Mean (SD)**	**n**	**Mean (SD)**	**OR (95% CI)**	**P value**
Age depression onset	2,120	31.9(14.5)	32,793	35.5(14.5)	0.98 (0.98-0.99)	P < 0.001
	n	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Severe depression	910	39.5	5,043	14.4	2.80(2.46-3.20)	P < 0.001
Recurrent depression	1,583	74.9	19,604	58.1	2.03(1.84-2.25)	P < 0.001
Duration of worst episode						
<1 month	76	3.3	2,177	6.3	Ref	
1 to 3 months	436	19.0	9,394	26.9	1.31(1.02-1.68)	P < 0.05
3 to 6 months	440	19.2	7,101	20.4	1.70(1.32-2.17)	P < 0.001
6 to 12 months	434	18.9	6,681	19.2	1.78(1.39-2.28)	P < 0.001
1 to 2 years	352	15.4	4,976	14.3	2.00(1.55-2.58)	P < 0.001
>2 years	554	24.2	4,528	13.0	3.45(2.70-4.41)	P < 0.001
Help seeking for depression	2,076	90.1	28,440	80.9	2.04(1.78-2.36)	P < 0.001

Note: Models are adjusted for age and gender

Table 3. Differences in lifestyle factors and adverse life events between persons with atypical depression and those with non-atypical depression

		Atypical Depression N=2,305		Non-Atypical Depression N=35,129			
Lifestyle factors		**n**	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Smoking	Never					Ref	
	Ever	1,117	48.7	16,448	46,9	1.15(1.06-1.26)	P < 0.01
Social isolation	No					Ref	
	Yes	293	12.9	3,534	10.2	1.32(1.16-1.51)	P < 0.001
Loneliness	No					Ref	
	Yes	223	10.1	2,144	6.3	1.74(1.50-2.01)	P < 0.001
Moderate physical activity	No					Ref	
	Yes	1,312	56.9	22,134	63.0	0.80(0.74-0.88)	P < 0.001
Childhood adversities							
Felt loved	Yes					Ref	
	No	378	16.5	3,780	10.8	1.61(1.43-1.80)	P < 0.001
Felt hated	No					Ref	
	Yes	645	28.1	6,229	17.8	1.67(1.52-1.84)	P < 0.001
Physical abuse	No					Ref	
	Yes	449	19.7	4,660	13.3	1.51(1.36-1.68)	P < 0.001
Sexual abuse	No					Ref	
	Yes	251	11.2	2,508	7.3	1.48(1.29-1.70)	P < 0.001
Had someone to take to doctor when needed as a child	Yes					Ref	
	No	263	11.5	2,684	7.7	1.57(1.37-1.80)	P < 0.001
Adulthood adversities							
Been in confiding relationship	Yes					Ref	
	No	450	19.9	5,135	14.9	1.40(1.26-1.57)	P < 0.001
Physical violence by partner	No					Ref	
	Yes	394	17.2	4,050	11.6	1.44(1.28-1.61)	P < 0.001
Belittlement by partner	No					Ref	
	Yes	837	36.5	9,212	26.3	1.48(1.36-1.62)	P < 0.001
Non-consensual sexual interference by partner	No					Ref	
	Yes	201	8.8	1,862	5.3	1.54(1.32-1.80)	P < 0.001
Unable to pay rent or mortgage	No					Ref	
	Yes	317	13.9	3,196	9.2	1.56(1.37-1.77)	P < 0.001
Catastrophic trauma	No					Ref	
	Yes	1,562	67.8	20,604	58.7	1.51(1.37-1.65)	P < 0.001

Note: Models are adjusted for age and gender. Catastrophic trauma is defined being attacked, mugged, robbed, exposed to violent crime, sexual assault, serious accidents, life-threatening illness, combat or war, violent death.

Table 4. Differences in psychiatric and physical comorbidities between persons with atypical depression and those with non-atypical depression

	Atypical Depression N=2,305		Non-Atypical Depression N=35,129			
Probable psychiatric diagnoses based on self-reported symptoms						
	n	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Wider Bipolar	166	7.4	1,384	4	1.86(1.58-2.21)	P < 0.001
Bipolar 1	118	5.3	813	2.4	2.24(1.83-2.73)	P < 0.001
Bipolar 2	38	1.7	417	1.2	1.29(0.99-1.95)	P = 0.06
GAD	754	60.2	7,690	44.3	1.82(1.62-2.04)	P < 0.001
PTSD	717	31.3	5,656	16.2	2.21(2.01-2.42)	P < 0.001
Self-reported psychiatric diagnoses						
Schizophrenia	14	0.6	71	0.2	3.19(1.78-5.70)	P < 0.001
Other psychosis	50	2.2	378	1.1	1.99(1.47-2.69)	P < 0.001
Panic attacks	413	17.9	4,142	11.8	1.60(1.43-1.79)	P < 0.001
Agoraphobia	40	1.7	327	0.9	1.91(1.37-2.67)	P < 0.001
Social phobia	135	5.9	1,006	2.7	2.07(1.71-2.49)	P < 0.001
Any other phobia	83	3.6	728	2.1	1.77(1.41-2.24)	P < 0.001
OCD	75	3.3	493	1.4	2.19(1.71-2.81)	P < 0.001
Anorexia nervosa	18	0.8	450	1.3	0.52(0.32-0.84)	P < 0.01
Bulimia nervosa	24	1.0	251	0.7	1.13(0.74-1.72)	P = 0.58
Binge-eating	116	5.0	355	1.0	4.67(3.76-5.81)	P < 0.001
ADHD	10	0.4	54	0.2	2.86(1.44-5.65)	P < 0.01
Autism spectrum disorder	16	0.7	106	0.3	2.30(1.30-3.90)	P < 0.01
Personality disorder	27	1.2	243	0.7	1.60(1.07-2.39)	P < 0.05
Any addiction	360	16.3	3,712	10.9	1,56(1.38-1.75)	P < 0.01
Substance Dependence	232	10.7	2,235	6.4	1.65(1.43-1.91)	P < 0.05
Alcohol Dependence	61	2.7	501	1.4	2.00(1.52-2.63)	P < 0.001
Self-harm	385	16.8	3,855	11.0	1.46(1.30-1.64)	P < 0.001
Self-harm with suicidal intention	219	59.5	2,152	58.0	1.15(0.92-1.44)	P = 0.21
Physical comorbidities						
Any long-standing illness	1,169	50.7	12,194	35.5	2.19(2.01-2.39)	P < 0.001
CVD	650	28.3	8,280	23.6	1.63 (1.48-1.80)	P < 0.001
Metabolic syndrome	194	8.4	1,656	4.7	2.39 (2.04-2.80)	P < 0.001
Body Mass Index						
Normal (< 18.5)	334	14.5	13,386	38.2	Ref.	
Underweight (18.5–24.9)	3	0.1	228	0.7	0.49(0.15-1.54)	P = 0.22
Overweight (25.0–29.9)	834	36.2	13,658	39.0	2.79(2.44-3.17)	P < 0.001
Obese (>30)	1,131	49.1	7,770	22.2	6.47(5.71-7.35)	P <0.001

Note: Models are adjusted for age and gender

Supplementary Table 1. Sociodemographic differences between persons with atypical depression versus depression with typical neurovegetative symptoms

		Atypical Depression N=2,305		Typical Depression N=12,660			
		n	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Age	45to54	625	27.1	2,324	18.4	Ref	
	55to64	1,051	45.6	5,002	39.5	0.78(0.70-0.87)	P < 0.001
	65to74	585	25.4	4,757	37.6	0.45(0.40-0.51)	P < 0.001
	75Plus	44	1.9	577	4.6	0.28(0.21-0.39)	P < 0.001
Gender	Female	1,732	75.1	9,575	75.6	Ref	
	Male	573	24.9	3,085	24.4	1.03(0.92-1.14)	P = 0.61
Education	None	113	5.0	794	6.3	Ref	
	Other(vocational)	89	3.9	700	5.6	0.89(0.66-1.20)	P = 0.45
	Secondary school	705	31.0	3,895	31.1	1.27(1.03-1.57)	P < 0.01
	A level	397	17.4	1,768	14.1	1.57(1.26-1.98)	P < 0.001
	Degree	974	42.8	5,378	42.9	1.27(1.03-1.57)	P < 0.05
Income	<£18,000	442	21.0	1,944	17.0	Ref	
	£18,000-30,000	511	24.3	2,798	24.4	0.80(0.69-0.92)	P < 0.01
	£30,000-52,000	597	28.4	3,270	28.6	0.80(0.70-0.92)	P < 0.01
	£52,000-100,000	457	21.8	2,709	23.7	0.74(0.64-0.85)	P < 0.001
	>£100,000	94	4.5	733	6.4	0.56(0.44-0.71)	P < 0.001
House ownership	Rent social	197	8.8	474	3.8	Ref	
	Rent private	120	5.4	366	3.0	0.78(0.61-1.02)	P = 0.07
	Own mortgage	1,078	48.3	5,483	44.3	0.47(0.39-0.56)	P < 0.001
	Own outright	839	37.6	6,062	49.0	0.33(0.27-0.40)	P < 0.001

Note: Atypical depression is defined as meeting the DSM-V criteria for MDD and reporting symptoms of hypersomnia and weight gain; depression with typical neurovegetative symptoms is defined as meeting the DSM-V criteria for MDD and reporting symptoms of hyposomnia and weight loss.

Supplementary Table 2. Differences in depression age of onset, severity, recurrence, episode duration, and help seeking between persons with atypical depression versus depression with typical neurovegetative symptoms

	Atypical Depression N=2,305		**Typical Depression** N=12,660			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**OR (95% CI)**	**P value**
Age depression onset	2,120	31.9(14.5)	12,051	36.1(14.1)	0.99 (0.99-0.99)	P < 0.001
	N	**%**	**N**	**%**	**OR (95% CI)**	**P value**
Severe depression	910	39.5	3,090	24.4	1.89 (1.72-2.08)	P < 0.001
Recurrent depression	1,583	74.9	6,786	55.8	2.26 (2.04-2.52)	P < 0.001
Duration of worst episode						
<1 month	76	3.3	654	5.2	Ref	
1 to 3 months	436	19.0	3,347	26.6	1.14(0.88-1.46)	P < 0.05
3 to 6 months	440	19.2	2,693	21.4	1.43(1.10-1.85)	P < 0.001
6 to 12 months	434	18.9	2,600	20.7	1.47(1.14-1.91)	P < 0.001
1 to 2 years	352	15.4	1,864	14.8	1.74(1.33-2.27)	P < 0.001
>2 years	554	24.2	1,410	11.2	3.56(2.74-4.61)	P < 0.001
Help seeking for depression	2,076	90.1	10,387	82.2	1.94(1.67-2.25)	P < 0.001

Note: Models are adjusted for age and gender

Supplementary Table 3. Differences in lifestyle factors and adverse life events between persons with atypical depression versus depression with typical neurovegetative symptoms

		Atypical Depression		Typical Depression			
		N=2,305		N=12,660			
Lifestyle factors		**n**	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Smoking	Never					Ref	
	Ever	1,117	48.7	5,962	47.2	1.11(1.01-1.21)	P < 0.05
Social isolation	No					Ref	
	Yes	293	12.9	1,233	9.8	1.37(1.20-1.58)	P < 0.001
Loneliness	No					Ref	
	Yes	223	10.1	668	5.4	1.74(1.50-2.01)	P < 0.001
Moderate physical activity	No					Ref	
	Yes	1,312	56.9	8,244	65.1	0.80(0.74-0.88)	P < 0.001
Childhood adversities							
Felt loved	Yes					Ref	
	No	378	16.5	1,311	10.4	1.66 (1.46-1.88)	P < 0.001
Felt hated	No					Ref	
	Yes	645	28.1	2,205	17.5	1.72(1.55-1.91)	P < 0.001
Physical abuse	No					Ref	
	Yes	449	19.6	1,762	13.9	1.40(1.25-1.57)	P < 0.001
Sexual abuse	No					Ref	
	Yes	251	11.2	971	7.8	1.42(1.22-1.65)	P < 0.001
Had someone to take to doctor when needed as a child	Yes					Ref	
	No	263	11.5	1,021	8.1	1.50(1.-1.73)	P < 0.001
Adulthood adversities							
Been in confiding relationship	Yes					Ref	
	No	450	19.9	1,799	14.5	1.47(1.31-1.65)	P < 0.001
Physical violence by (ex)partner	No					Ref	
	Yes	394	17.2	1,641	13.0	1.33(1.18-1.50)	P < 0.001
Belittlement by (ex)partner	No					Ref	
	Yes	837	36.5	3,562	28.2	1.41(1.28-1.55)	P < 0.001
Non-consensual sexual interference by (ex)partner	No					Ref	
	Yes	201	8.8	744	5.9	1.49(1.26-1.75)	P < 0.001
Unable to pay rent or mortgage	No					Ref	
	Yes	317	13.9	1,226	9.8	1.46(1.28-1.67)	P < 0.001
Catastrophic trauma	No					Ref	
	Yes	1,562	67.8	7,232	57.1	1.56(1.42-1.71)	P < 0.001

Note: Models are adjusted for age and gender. Catastrophic trauma is defined being attacked, mugged, robbed, exposed to violent crime, sexual assault, serious accidents, life-threatening illness, combat or war, violent death.

Supplementary Table 4. Differences in psychiatric and physical comorbidities between persons with atypical depression versus depression with typical neurovegetative symptoms

	Atypical Depression N=2,305		Typical Depression N=12,660			
Probable psychiatric diagnoses based on self-reported symptoms						
	n	**%**	**n**	**%**	**OR (95% CI)**	**P value**
Wider Bipolar	166	7.4	536	4.3	1.66(1.39-2.00)	P < 0.001
Bipolar I	118	5.3	324	2.6	1.94(1.56-2.42)	P < 0.001
Bipolar II	38	1.7	154	1.2	1.32(1.92-1.89)	P = 0.13
GAD	754	60.2	2,884	45.9	1.70(1.50-1.93)	P < 0.001
PTSD	717	31.3	1,970	15.6	2.28(2.06-2.53)	P < 0.001
Self-reported psychiatric diagnoses						
Schizophrenia	14	0.6	25	0.2	2.79(1.43-5.44)	P < 0.01
Other psychosis	50	2.2	140	1.1	1.90(1.37-2.65)	P < 0.001
Panic attacks	413	17.9	1,663	13.1	1.43(1.27-1.61)	P < 0.001
Agoraphobia	40	1.7	119	0.9	1.93(1.34-2.79)	P < 0.001
Social phobia	135	5.9	338	2.7	2.12(1.72-2.61)	P < 0.001
Any other phobia	83	3.6	263	2.1	1.81(1.41-2.33)	P < 0.001
OCD	75	3.3	164	1.3	2.32(1.76-3.07)	P < 0.001
Anorexia nervosa	18	0.8	243	1.9	0.38(0.23-0.61)	P < 0.001
Bulimia nervosa	24	1.0	105	0.8	1.02(0.65-1.61)	P = 0.90
Binge-eating	116	5.0	64	0.5	10.06(7.36-13.75)	P < 0.001
ADHD	10	0.4	19	0.2	2.65(1.22-5.77)	P < 0.05
Autism spectrum disorder	16	0.7	21	0.2	3.43(1.77-6.64)	P < 0.001
Personality disorder	27	1.2	88	0.7	1.49(0.96-2.31)	P = 0.07
Any addiction	360	16.3	1,222	9.9	1.65(1.45-1.88)	P < 0.001
Substance Dependence	232	10.7	759	6.00	1.65(1.41-1.93)	P < 0.001
Alcohol Dependence	61	2.7	178	1.4	1.79(1.32-2.42)	P < 0.001
Self-harm	385	16.8	1,397	11.1	1.47(1.30-1.67)	P < 0.001
Suicidal intention among self-harmers	219	59.5	801	59.8	1.04(0.82-1.32)	P = 0.21
Physical comorbidities						
Any long-standing illness	1,169	50.7	4,032	32.5	2.46(2.25-2.70)	P < 0.001
CVD	650	28.3	2,608	20.6	1.92(1.72-2.13)	P < 0.001
Metabolic syndrome	194	8.4	401	3.2	3.48(2.90-4.18)	P < 0.001
Body Mass Index (kg/m^2)						
Normal (< 18.5)	334	14.5	5,909	46.8	Ref.	
Underweight (18.5–24.9)	3	0.1	116	0.9	0.44(0.14-1.40)	P = 0.16
Overweight (25.0–29.9)	834	36.2	4,614	36.5	3.58(3.13-4.10)	P < 0.001
Obese (>30)	1,131	49.1	1,998	15.8	11.34(9.91-12.99)	P <0.001

Note: Models are adjusted for age and gender

Supplementary Table 5. Tetrachoric correlations between individual depressive symptoms among persons with lifetime probable MDD

	Weight gain	Hypersomnia	Weight loss	Hyposomnia	Concentration	Tiredness	Interest loss	Sadness	Worthlessness	Death thoughts
Weight gain	1.00									
Hypersomnia	0.20***	1.00								
Weight loss	N/A	-0.20***	1.00							
Hyposomnia	0.06***	N/A	-0.14***	1.00						
Concentration	-0.04*	0.07***	-0.04*	-0.09***	1.00					
Tiredness	0.21***	0.34***	-0.18***	0.01	0.22***	1.00				
Interest loss	0.06***	0.26***	-0.08***	0.04**	0.07***	0.13***	1.00			
Sadness	-0.08**	0.02	-0.06*	-0.02	0.01	-0.13*	N/A	1.00		
Worthlessness	0.13***	0.20***	-0.16***	0.02*	0.15***	0.09***	0.17***	0.21***	1.00	
Death thoughts	0.01	0.04***	0.02*	-0.08***	0.01	-0.08***	0.03*	0.07**	0.14***	1.00

* $p < 0.05$; ** $p < 0.01$; ***$p < 0.001$; the correlation between sadness and interest loss could not be computed because there are no depressed persons with a score of zero on both sadness and interest loss given that the MDD criteria require the presence of at least one of the two symptoms.

Supplementary Table 6: Question and Answer Format of the UK Biobank Mental Health Questionnaire

Variable	Question Asked	Possible Answers
Sociodemographic factors		
Age	Please confirm your month & year of birth	mm yyyy
Gender	Please confirm your sex	0 = Female 1 = Male
Education	Which of the following qualifications do you have?	0 = None of the above 1 = Other 2 = GCSE 3 = A Level 4 = Degree
Income	What is the average total income before tax received by your household?	0 = <£18,000 1 = £18,000-30,000 2 = £30,000-52,000 3 = £52,000-100,000 4 = >£100,000 UN = Do not know DA = Prefer not to answer
House ownership	Do you own or rent the accommodation that you live in?	1= Rent social 2 = Rent private 3 = Own mortgage 4 = Own outright UN = Do not know DA = Prefer not to answer
Risk factors and life events		
Smoking	Do you smoke tobacco now? (i.e., during the baseline UKB assessments) In the past, how often have you smoked tobacco?	0 = No 1 = Yes, on most or all days 2 = Only occasionally 3 = Prefer not to answer 0 = I have never smoked 1 = Just tried once or twice 2 = Smoked occasionally 3 = Smoked on most or all days 4 = Prefer not to answer A binary variable was derived for smoking status: 0 = Never smoked, if current smoker = 0 and past smoker < 2; 1 = Ever smoker, if current smoker = 1 and/or past smoker > 1
Moderate physical activity	In a typical week, on how many days did you do 10 minutes of moderate physical activities like carrying light loads, cycling at normal pace? (do not include walking)	A binary variable was generated: 1 = 10 minutes of moderate physical activities at least 3 days a week; 0 = 10 minutes of moderate physical activities less than 3 days a week;

Social isolation	(1) “Including yourself, how many people are living together in your household? Include those who usually live in the house such as students living away from home during term time, partners in the armed forces or professions such as pilots”; (2) “How often do you visit friends or family or have them visit you? (3) “Which of the following [leisure/social activities] do you engage in once a week or more often?”.	1 point for living alone 1 point for friends and family visit less than once a month 1 point for no participation in social activities at least weekly Total score 0=3 A binary variable was derived: 0 = no social isolation, if total score ≤ 1 1 = social isolation, if total score ≥ 2
Loneliness	(1) “Do you often feel lonely?” (2) “How often are you able to confide in someone close to you?” Elovainio, M., C. Hakulinen, et al. "Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study." The Lancet Public Health **2**: e260-e266.	0 = No 1 = Yes 0 = almost daily to once every few months 1 = never or almost never A binary variable was derived. Lonely|: total score = 2 Not lonely|: total score < 2
Childhood adverse events	Includes 1 question from each domain of the Childhood Trauma Questionnaire. *Walker, E. A., et al. (1999). "Adult health status of women with histories of childhood abuse and neglect." The American Journal of Medicine **107**(4): 332-339*	0 = Never true 1 = Rarely true 2 = Sometimes true 3 = Often 4 = Very often true DA = Prefer not to answer Binary variables were derived based on the following thresholds: 20489 Felt loved as a child < 2 OR 20488 Physically abused by family as a child ≥2 OR 20487 Felt hated by family member as a child ≥2 OR 20490 Sexually molested as a child ≥2 OR 20491 Someone to take to doctor when needed as a child < 3
Adult adverse events	Based on answers to the five questions of Adult Trauma Screen (written for this questionnaire).	0 = Never true 1 = Rarely true 2 = Sometimes true

		3 = Often 4 = Very often true DA = Prefer not to answer Binary variables were derived based on the following thresholds: 20522 Been in a confiding relationship as an adult < 2 20523 Physical violence by partner or ex-partner as an adult ≥ 2 20521 Belittlement by partner or ex-partner as an adult ≥2 20524 Sexual interference by partner or ex-partner without consent as an adult ≥2 20525 Able to pay rent/mortgage < 3
Catastrophic trauma	In your life, have you: a) Been a victim of a sexual assault, whether by a stranger or someone you knew? b) Been attacked, mugged, robbed, or been the victim of a physically violent crime? c) Been in a serious accident that you believed to be life-threatening at the time? d) Witnessed a sudden violent death (eg. murder, suicide, aftermath of an accident)? e) Been diagnosed with a life-threatening illness? f) Been involved in combat or exposed to a war-zone (either in the military or as a civilian)?	Endorsed one or more events from checklist 0 = Never 1 = Yes, but not in the last 12 months 2 = Yes, within the last 12 months DA = Prefer not to answer A binary variable was derived 0 = Never 1 = Ever (experienced 1 or several catastrophic events within the last 12 months or before)
Depression Features		
Depression age of onset	Regarding times in your life when you have had feelings of depression or loss of interest: About how old were you the FIRST time you had a period of two weeks like this? (Whether or not you received any help for it.)	Record years of age when first felt this way UN = Do not know DA = Prefer not to answer
Severe depression	Meets criteria for a lifetime diagnosis of MDD (see Depression Ever below) and reports all 8/8 symptoms of depression assessed with CIDI-SF and reports a lot of impairment.	A binary variable was derived: 1 = severe MDD 0 = non-severe MDD
Recurrent depression	Regarding times in your life when you have had feelings of depression or loss of interest: How many periods did you have in your life lasting two or more weeks where you felt like this?	Text box for number. 1 = single depression episode 2 and above = recurrent depression episodes
Depression duration	Please think of the two-week period in your life when your feelings of	1 = less than a month 2 = between one and three months

	depression or loss of interest were worst. About how long did you feel this way?	3 = over three months, but less than six months 4 = over six months, but less than 12 months 5 = one to two years 6 = over two years
Help seeking for depression	Regarding times in your life when you have had feelings of depression or loss of interest: Did you ever tell a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)	0 = No 1 = Yes UN = Do not know DA = Prefer not to answer
Psychiatric comorbidities based on self-reported diagnoses		
Clinical diagnoses based on self–reports (A)	Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently? (tick all that apply): By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis	[Select up to seven from] 0 = None of the above 1 = Depression 2 = Mania, hypomania, bipolar or manic-depression 3 = Anxiety, nerves or generalized anxiety disorder 4 = Social anxiety or social phobia 5 = Agoraphobia 6 = Any other phobia (e.g. disabling fear of heights or spiders 7 = Panic attacks 8 = Obsessive compulsive disorder (OCD) DA = Prefer not to answer
Clinical diagnoses based on self–reports (B)	Have you been diagnosed with one or more of the following~~;~~ mental health problems by a professional, even if you don't have it currently? (tick all that apply): By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis.	[Select up to eight from] 0 = None of the above 1 = Anorexia nervosa 2 = Bulimia nervosa 3 = Psychological over-eating or binge-eating 4 = Schizophrenia 5 = Any other type of psychosis or psychotic illness 6 = A personality disorder 7 = Autism, Asperger's or autistic spectrum disorder 8 = Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD) DA = Prefer not to answer
Any addiction	Have you ever been addicted to or dependent on one or more things, including substances (not cigarettes/coffee) or behaviors (such as gambling)?	1 = Yes 0 = No UN = Do not know DA = Prefer not to answer
Substance Dependence:	Have you been addicted to or dependent on prescription or over-the-counter medication? Have you been addicted to illicit or recreational drugs?	1 = Yes 0 = No UN = Do not know DA = Prefer not to answer 1 = Yes 0 = No

		UN = Do not know DA = Prefer not to answer *Note:* Substance dependence is a subcategory of any addiction
Alcohol Dependence:	Have you been physically dependent on alcohol? This means experiencing withdrawal symptoms, such as sweating, shaking and nausea, if you didn't drink.	1 = Yes 0 = No UN = Do not know DA = Prefer not to answer *Note:* Alcohol dependence is a subcategory of substance dependence
Self-harm behaviours	Have you contemplated harming yourself (for example by cutting, biting, hitting yourself or taking an overdose)? Have you deliberately harmed yourself, whether or not you meant to end your life?	0 = No 1 = Yes, once 2 = Yes, more than once DA = Prefer not to answer 0 = No 1 = Yes DA = Prefer not to answer
Self-harm with suicide attempt	Have you harmed yourself with the intention to end your life?	0 = No 1 = Yes DA = Prefer not to answer
Physical comorbidities		
Long-standing illness	Do you have any long-standing illness, disability or infirmity?	0 = No 1 = Yes UN = Do not know DA = Prefer not to answer
Metabolic syndrome	Participants were classified as having metabolic syndrome if: - Their waist circumference was: ≥ 102 cm for males and ≥ 88 cm for females; - They had any two of the following: diabetes, hypertension, hypercholesterolemia.	
Diabetes	**Q1:** Has a doctor ever told you that you have diabetes? **Q2:** Do you regularly take any of the following medications? (you can select more than one answer)	0 = No 1 = Yes UN = Do not know DA = Prefer not to answer 1 = cholesterol lowering medication 2 = blood pressure medication 3 = insulin UN = Do not know DA = Prefer not to answer Participants were considered as diabetes cases if they answered Q1 = 1 and/or Q2 = 3.

Hypertension	**Q1:** Has a doctor ever told you that you have high blood pressure? **Q2:** Do you regularly take any of the following medications? (you can select more than one answer)	0 = No 1 = Yes UN = Do not know DA = Prefer not to answer 1 = cholesterol lowering medication 2 = blood pressure medication 3 = insulin UN = Do not know DA = Prefer not to answer Participants were considered as hypertension cases if they answered Q1 = 1 and/or Q2 = 2.
Hypercholesterolemia	**Q1:** Has a doctor ever told you that you have hypercholesterolemia **Q2:** Do you regularly take any of the following medications? (you can select more than one answer)	0 = No 1 = Yes UN = Do not know DA = Prefer not to answer 1 = cholesterol lowering medication 2 = blood pressure medication 3 = insulin UN = Do not know DA = Prefer not to answer Participants were considered as hypertension cases if they answered Q1 = 1 and/or Q2 = 1.
Cardiovascular disease	Has a doctor ever told you that you have had any of the following conditions? (You can select more than one answer)	1 = Heart attack 2 = Angina 3 = Stroke 4 = High blood pressure 0 = None of the above DA = Prefer not to answer A binary variable was derived: 0 = None 1 = any of the above

Supplementary Table 7. Case and control criteria derived from the UK Biobank Mental Health Questionnaire

Disorder - case and control definitions	Fields and codes	Notes and references
Case: Lifetime depression	At least one core symptom of depression, most or all of the day on most or all days for a two-week period, with at least five depressive symptoms that represent a change from usual occurring over the same time-scale, with some or a lot of impairment. Persistent sadness (20446) = Yes OR Loss of interest (20441) = Yes AND How much of day (20436) = Most of day or All day long AND Did you feel this way (20439) = Almost every day or Every day AND Impairment (20440) = Somewhat or A lot AND Total number of symptoms endorsed (core and others) >= 5 Persistent sadness (core) 20446; Loss of interest (core) 20441; Tired or low energy 20449; Gain or loss of weight 20536 = Gain, Loss or Gain and loss; Sleep change 20532; Trouble concentrating 20435; Feeling worthless 20450; Thinking about death 20437	CIDI-SF (Composite International Diagnostic Interview – Short Form), depression module, lifetime version. Scored based on DSM definition of major depressive disorder *Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen HU (1998). The World Health Organization composite international diagnostic interview* *Int. J. Methods Psychiatr Res, 7(4):171-85.*
Control: Lifetime depression	Not endorsing depression or screening positive on PHQ or CIDI NOT (reported diagnosis of depression 20544 or 20002) AND NOT Core symptoms from above AND PHQ score ≤5	Case plus control plus subthreshold should include all participants with valid responses. By excluding subthreshold symptoms, we can be confident that this group has not experienced a classical depressive episode
Case: Lifetime bipolar disorder type I:	Ever manic/hyper or irritable, plus at least three other features (four if never manic/hyper), plus duration a week or more, plus symptoms caused significant problems. Requires also to be case for depression ever. Case {depression ever} AND High/Hyper 20501 = 01 OR Irritable 20502 = 01 AND Four features from: □ High/Hyper 20501; Active 20548(01); Talkative 20548(02); Less sleep 20548(03); Creative/ideas 20548(04); Restless	Case for depression is not required in DSM-IV diagnostic criteria, but it is added here to improve the positive predictive value of the test (see text and references). This definition does not exclude antidepressant-induced mania. *Cerimele et al. (2014). The prevalence of bipolar disorder in primary care samples: a systematic review, General Hospital Psychiatry 36: 19-25* *Carvalho, A. F., Y. Takwoingi, et al. (2015). "Screening for bipolar spectrum disorders: a comprehensive*

	20548(5); Confident 20548(55); Thoughts racing 20548(7); Easily distracted 20548(8) AND Duration 20492 = A week or more AND Symptoms caused problem 20493 = yes	*meta-analysis of accuracy studies." Journal of affective disorders **172**: 337-346*
Variant: Lifetime bipolar type II:	As above, without disruption from symptoms Case {depression ever} AND High/Hyper 20501 = 01 OR Irritable 20502 = 01 AND Four features as above AND Duration 20492 = A week or more	There is less agreement over the definition of bipolar affective disorder type II. DSM-IV criteria require symptoms for four days or more. Here is one week, so could be predicted to miss some cases.
Control: Hypomania / Mania	NOT {hypomania/mania} AND NOT {categorised bipolar on last UKB categorisation 20126 = 1 or 2} AND NOT {self-reported bipolar 20544=10}	
Case: Lifetime GAD	Excessive worrying about a number of issues, occurring most days for six months and difficult to control, with three or more somatic symptoms and functional impairment. Worried tense of anxious (20421) = Yes AND Duration (20420) >= 6 months or All my life AND Most days (20538) = Yes AND Excessive: More than most (20425) OR Stronger than most (20542) AND Number of issues: More than one thing (20543) OR Different worries (20540) AND Difficult to control: Difficult to stop worrying (20541) OR Couldn't put it out of mind (20539) OR Difficult to control (20537) AND Functional impairment: Role interference (20418) = Some or A lot AND 3 somatic symptoms out of: Restless. 20426; Keyed up or on edge. 20423; Easily tired. 20429; Having difficulty keeping your mind on what you were doing. 20419; More	CIDI-SF (Composite International Diagnostic Interview – Short Form), GAD module, lifetime version. Scored based on DSM definition of GAD *Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen HU. The World Health Organization composite international diagnostic interview* *short-form (CIDI-SF). Int J Methods Psychiatr Res. 1998;7(4):171-85.* *National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder in adults: management. NICE Clinical Guideline CG113 (available at https://www.nice.org.uk/guidance/cg113) 2011*

	irritable than usual. 20422; Having tense, sore, or aching muscles. 20417; Often having trouble falling or staying asleep. 20427	
Control: Lifetime GAD	Not meeting criteria for GAD ever nor scoring over low cut-off for GAD-7 NOT case {GAD ever} AND GAD-7 score < 5	Excluding those that screen positive for mild anxiety means that there is greater confidence that this group have not had anxiety disorder
Case: Current PTSD	Case: PCL-6 sum of scores ≥ 14 Sum of scores on questions representing the core symptoms of PTSD (scored 1-5) {20497Repeated disturbing thoughts of stressful experience in past month 20498Felt very upset when reminded of stressful experience in past month 20495Avoided activities or situations because of previous stressful experience in past month 20496Felt distant from other people in past month 20494Felt irritable or had angry outbursts in past month} + 20508 Trouble concentrating (scored 1-4) (nb biobank coded 0-4, subtract 5 to adjust)	Does not currently require catastrophic trauma, but it refers to "stressful event" in the text of the questions as this is not an exhaustive list of possible traumatic events. Using PHQ item for concentration, scores out of 29 (conventionally scores out of 30), and will make it slightly harder to reach conventional threshold. *Lang AJ, Stein MB (2005).An abbreviated PTSD checklist for use as a screening instrument in primary care. Behaviour Research and Therapy,43(5):585-94*
Control: Current PTSD	PCL-6 sum of scores 13 or less.	*Note:* "Current" PTSD refers to persons meeting the criteria for PTSD when completing the MHQ assessments.